## REMARKS

Reconsideration is requested.

Claims 1-79, 85, 86, 117 and 118 have been canceled, without prejudice. Claims 80-84, 87-116 and 119-173 are pending.

The claims have been revised, without prejudice.

The Examiner indicates that claims 80-173 are pending and under examination. The Examiner has maintained the restriction requirement of April 17, 2007 and made the requirement final. Reconsideration and withdrawal of the lack of unity determination and election requirement are requested in view of the above amendments, which are believed to moot the basis for the election requirement, and the following remarks.

Absent the Examiner's withdrawal of the election requirement, the Director is requested to grant the attached Rule 181 Petition and direct the Examiner to withdraw the lack of unity determination and examine the full breadth of the claims. The attached Rule 181 Petition is believed to be timely filed, pursuant to 34 CFR § 1.144 and MPEP § 821. A fee is not believed to be required for consideration of the Rule 181 Petition as the same is only believed to be required due to the Examiner's error. The Office is authorized however, such as by the attached Transmittal Letter, to charge the undersigned's Deposit Account 14-1140 for any fee required for consideration of the attached Rule 181 Petition.

The Examiner's election requirement of April 17, 2007 asserted the claims contained the following allegedly separately patentable Groups of subject matter:

Group I. Claims 80-140, 143, 146-1 63 and 165-1 73 drawn to carbarnic acid piperazine compounds when Cy is a pyridine, methods of treating and compositions of these compounds.

Group II. Claims 80-140, 143, 146 and 165-1 73 drawn to carbamic acid piperazine compounds when Cy is a pyrimidine, methods of treating and compositions of these compounds.

Group III. Claims 80- 140, 143, 146- 163 and 165- 173 drawn to carbamic acid piperazine compounds when Cy is a bicyclic ring containing one nitrogen atom (that is benzopyrrole), methods of treating and compositions of these compounds.

Group IV. Claims 80- 140, 143, 146- 163 and 165- 173 drawn to carbamic acid piperazine compounds when Cy is a bicyclic ring containing one or more chalcogens (that is benzofuran or benzothiophene), methods of treating and compositions of these compounds.

Group V. Claims 80-173, drawn to carbamic acid piperazine compounds which do not fall within the scope of Groups I to V, methods of treating and compositions of these compounds.

The applicants elected the subject matter of the Examiner's Group V, with traverse, in the Response of May 17, 2007.

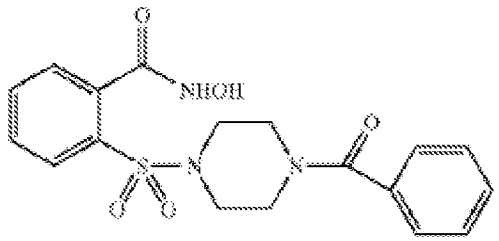
The basis of the Examiner's lack of unity of invention assertion was that

> "the inventions listed as Groups I to V do not relate to a single general inventive concept under 35 USC 121 or PCT Rule 13.1 because:
> …
> at least one Markush alternative is not novel because prior art by Bedell, L., et al., U.S. 6,380,258 and U.S. 7,115,632 anticipates group V, thus the lacking of unity of invention has

been found." See pages 3-4 of the Office Action of April 17, 2007.[1]

The pending claims are submitted to be patentable over U.S. Patent No. 7,115,632, as well as U.S. Patent Nos. 6,696,449 and 6,683,078 for at least the following reasons.

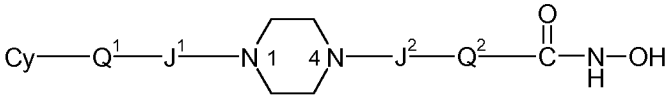
The Examiner is understood to believe that the following compound described in column 38, lines 5-10 of U.S. Patent No. 7,115,632, allegedly anticipates claims 80, 81, 85, 98, 116, 117, 138-141, 145, 146, 163, 164 and 168:



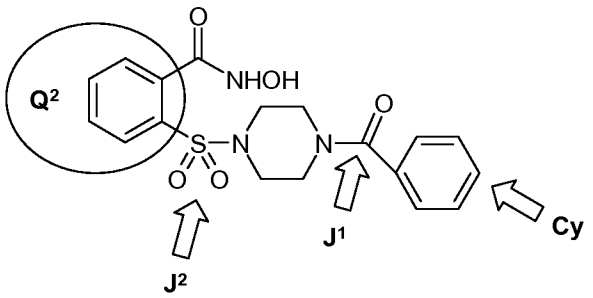

The Examiner asserts that the "same compound is also found in" U.S. Patent Nos. 6,696,449 and 6,683,078 . See page 12 of the Office Action dated July 19, 2007.

[1] The Office Action of July 19, 2007 confirms, in contradiction to the alleged basis for the lack of unity determination, that the elected subject matter (i.e., the subject matter of the Examiner's Group V) is patentable over U.S. Patent No. 6,380,258. The applicants note in this regard however that the application from which U.S. Patent No. 6,380,258, issued is a grand-parent of the application from which U.S. Patent No. 7,115,632 issued. The Examiner is again requested to make U.S. Patent No. 6,380,258, of record by listing the same on a PTO -892 Form. See Response filed May 17, 2007.

Claim 80, for example, however provides a compound of the following formula:




When compared with the compound cited by the Examiner, the applicants believe that the -$Q^2$- group of the claimed structure is a 1,2-phenylene group in the cited compound of the cited art. More specifically, the following reproduction of the structure cited by the Examiner identifies what are believed to be structures corresponding to the claimed structures:



The 1,2-phenylene group of the structure of the cited art, corresponding to $-Q^2-$ of the claimed structures, is believed to be an example of a $C_{5-20}$arylene group.

The pending claims do not include compounds however wherein $-Q^2-$ is a $C_{5-20}$arylene group or other group corresponding to a structure of the cited compound of the cited art.

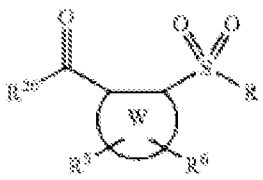
The claims are submitted to be novel over the teachings of U.S. Patent No. 7,115,632 which was the basis for the alleged lack of unity determination. The claims are similarly patentable over "The same compound found in" U.S. Patent Nos. 6,696,449 and 6,683,078.

Withdrawal of the lack of unity of invention and examination of all of the claimed subject matter are requested.

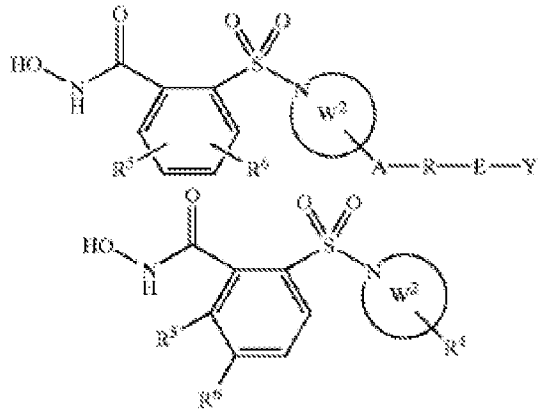
Alternatively, grant of the attached Rule 181 Petition and withdrawal of the lack of unity of invention by the Director and examination of all of the claimed subject matter by the Examiner are requested.

For completeness, the applicants note that each of the three cited patents require the above-noted 1,2-phenylene group.

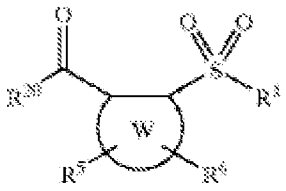
Specifically, U.S. Patent No. 7,115,632 describes compounds of the following formula:



U.S. Patent No. 6,696,449 describes compounds of the following formula:



U.S. Patent No. 6,683,078 describes compounds of the following formula:



The pending claims do not include $Q^2$ as a $C_{5-20}$arylene.

The claims are patentable over the cited art.

Withdrawal of the lack of unity of invention and examination of all of the claimed subject matter are requested.

Alternatively, grant of the attached Rule 181 Petition and withdrawal of the lack of unity of invention by the Director and examination of all of the claimed subject matter by the Examiner are requested.

Withdrawal of the Section 102 rejections of claims 80, 81, 85, 98, 102, 116, 117, 138-141, 145, 146, 163, 164 and 168 over Bedell (U.S. Patent No. 7,115,632), McDonald, et al., U.S. Patent No. 6,696,449 and McDonald, et al., U.S. Patent No. 6,683,078, is requested for the same reasons noted above.

To the extent not obviated by the above amendments, the Section 112, first paragraph "enablement", rejections of claims 80-173 are traversed. Reconsideration and withdrawal of the rejections are requested in view of the above and the following comments.

Initially, the applicants note that claims are not lacking in enabling support where one would require routine experimentation to make and use the claimed invention. The "calculation of the number of compounds embraced in the instant claim 80" is not believed to be relevant to the issue of enablement. See page 4, first paragraph, of the Office Action dated July 19, 2007. The Examiner's assertion that the claimed genus is "too large" is not believed to be a basis for rejecting the claims under Section 112, first paragraph. Id.

The Examiner has also asserted that the claimed prodrugs and solvates are allegedly not supported by an enabling disclosure. The rejection is moot in view of the

above with regard to produgs. The rejection is traversed with regard to solvates and consideration of the following in this regard is requested.

Claims 80-173 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for (hydrates and) solvates of the compounds of the claimed invention. Applicants respectfully traverse the rejection because (hydrates and) solvates are well enabled under the patent laws.

The Examiner is understood to have acknowledged that the claimed pharmaceutically acceptable salts are supported by an enabling disclosure.

The specification is required to teach one of ordinary skill in the art how to make and use the claimed invention without undue experimentation. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. Id. at 1404.

The issue in In re Wands was whether the applicant had enabled one of ordinary skill in the art to make high-affinity IgM antibodies against HbsAg that were needed to practice the claimed invention. Id. at 1402. The Examiner had rejected the claims as allegedly not being enabled by the specification due to the alleged unpredictability and unreliability of the production of high-affinity IgM anti-HBsAg antibodies. The Examiner asserted that production of the required antibodies would have allegedly required undue experimentation. Id.

The Federal Circuit reversed, explaining that even though screening for hybridomas was labor-intensive with a number of steps (e.g., immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells, cloning the

hybridoma, screening the resulting antibodies, etc.), all the methods needed to practice the invention were well known, and "the amount of effort needed to obtain" the antibodies was not excessive so as to be undue. Id. at 1407.

The preparation of hydrates and solvates of a given organic molecule is substantially easier, and experimentation more routine, than the production of antibodies considered by the Wands court. The process of preparing hydrates and solvates requires significantly fewer steps, and demands much less experimentation than for the preparation of a monoclonal antibody considered by the Wands court.

By analogy therefore, if the Wands court concluded that the preparation of the monoclonal antibody under consideration was enabled despite the complex and lengthy process involved, the applicants believe the court would similarly find the production of the claimed solvates as being supported by an enabling disclosure, especially in view of the generally advanced level of skill in the art regarding the same.

The following Table provides a step-by-step comparison of some of the major steps involved in the production of a monoclonal antibody (as disclosed in In re Wands, 8 USPQ2d 1407) and the one step involved in making a solvate of the claims.

**Table[2]**

| Step | Monoclonal Antibody | Hydrate or Solvate |
|---|---|---|
| 1 | immunize animal | expose the compound to water or solvent |
| 2 | remove the spleen from the immunized animal | |

[2] In Applicants own experience, there are several other steps in the production of monoclonal antibodies not described in *Wands*, e.g., preparation of antigen, repeated immunization of animals, testing of animal serum for the presence and titer of the antibodies of choice, introduction of hybridoma cells into animals to induce liquid ascytes tumours, draining the ascytes tumors from the livings animals, purification of monoclonal antibodies from the ascytes fluids, etc.

| | | |
|---|---|---|
| 3 | separate the lymphocytes from the other spleen cells | |
| 4 | mix the lymphocytes with myeloma cells | |
| 5 | treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody | |
| 6 | separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive | |
| 7 | culture single hybridoma cells (often 100 of different cells) in separate chambers | |
| 8 | assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen | |
| Total Time | Months | About 1-2 days |

As is clearly shown in the above Table, the process of production of a monoclonal antibody is more complex and time-consuming than the production of a hydrate or solvate. Given the findings by the Wands court, the applicants believe the court would also find the production of solvates of the claims to require less than undue experimentation.

While the complexity of the procedures for making monoclonal antibodies and hydrates/solvate is highly disparate, the processes share the characteristic that the step(s) involved are well-known and routine.

Specifically, production of hydrates and solvates, samples of an organic compound are exposed to water or various solvents. Once the hydrates and solvates are formed, they can be readily analyzed by routine methods such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light

microscopy, and hot stage microscopy (see page 18, right column, Vippagunta et al. *Advanced Drug Delivery Reviews* 48 (2001) 3-26, copy attached) or other routine techniques to detect and quantify the presence of hydrate or solvate molecules in the sample. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent.

The applicants submit, with due respect to the Examiner, that placing a powder on a dish and letting it sit out on a humid day, as one means of making a hydrate, requires no undue experimentation. Other routine procedures for making and identifying hydrates and solvates are described, for example, on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: *Polymorphism in Pharmaceutical Solids*, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999 (copy attached).

While there may be many solvents and conditions to attempt, and number of species may be large, screening the products requires routine methods that are very well known in the art . In fact, there are numerous companies that routinely provide this screening service (usually combined with polymorph screens) and advertise how quickly and efficiently they can identify hydrates and solvates. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam), and Aptuit (Greenwich, CT).

The methods required to make the claimed solvates and hydrates are well known and routine in the art. Withdrawal of the Section 112, first paragraph "enablement", rejection relating to the recitation of solvates is requested.

The Examiner is understood to believe that page 365 of West (*Solid State Chemistry and its Applications* supports a conclusion that hydrate/solvate formation is allegedly unpredictability , that there is allegedly a lack of sufficient direction or guidance to make hydrates or solvates including an alleged lack of working examples in the present specification, and that the production of solvates allegedly requires a large quantity of experimentation.

Initially, the applicants note that the cited reference was published nearly 20 years ago and is not believed to reflect the level of skill in the art at the relevant time.

A review of the claims issued in U.S. patents since 1976 through a "quick search" of the U.S. Patent Office on-line records indicates that there have been 3233 patents issued by the Patent Office containing the word "solvate" in the claims. The following U.S. Patents, for example, were readily identified as having claims including hydrates and solvates: U.S. Patent Nos. 7,232,823; 7,230,024; 7,230,002; 7,229,991; 7,227,027; 7,211,591; 7,173,037; 7,157,466; 7,105,523; 6,946,476, and 6,946,458. Solvate formation is well known in the art and claims to the same have been granted by the Patent Office in recognition of the same.

The passage relied on by the Examiner in the cited passage of West relates to the "predictability" of whether a solid solution will form. The Examiner's reliance on West in this regard however is believed to be the basis of rejection which the Wands court found unsupportable in rejecting Wands' claims for an alleged lack of enablement.

The applicants believe the court would similarly find the present Examiner's reliance on West to be insufficient to sustain a rejection for an alleged lack of enablement.

The applicants understand that the alleged unpredictability due to a low success rate of preparing monoclonal antibodies was rejected by the Wands court as a basis for rejecting the Wands' claims for an alleged lack of enablement. The Wands court is understood to have found that all the methods needed to make the products used in the claimed method were well known and that the amount of effort was not undue despite what might have been a large amount of experimentation needed.

The Wands court is understood to have believed that even though the preparation of a monoclonal antibody involved unpredictable outcomes, the unpredictability has little weight against the fact that if an antibody could be made, it would almost certainly be made by the routine methods known in the art. By analogy, while the outcome of every feature and characteristic of a hydrate or solvate of a given compound, such as the hygroscopicity, solvent/water content, type of hydrate/solvate (e.g., channel, isolated sites, etc.) may not be absolutely predictable, the production of the same however is well known and requires no more than routine experimentation.

Moreover, the success rate for making a hydrate or solvate may not be 100%. However, like for antibodies, if a solvate or hydrate could be made, it would almost certainly be made by the routine methods for making hydrates and solvates that are well-known in the art. Accordingly, any unpredictability associated with hydrate or solvate formation that might exist, as suggested in West and Vippagunta et al., is clearly outweighed by the fact that preparing and screening for hydrates and solvates is routine and employs well-known methods.

With respect to the allegations of lack of sufficient direction or guidance and lack of working examples, Applicants respectfully note that the courts have held that what is well known in the art need not be taught in the application. Lindemann Maschinenfabrik v. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). The courts have further held that working examples are not necessary if the disclosure is such that one skilled in the art can practice the claimed invention. In re Borkowski, 164 USPQ 642 (C.C.P.A. 1970); Ex parte Nardi, 229 USPQ 79 (Pat. Off. Bd. App. 1986).

The Examiner appears to conclude that because no hydrates or solvates are exemplified in the application, they must not exist, and thus there is allegedly inadequate guidance and no working examples. See paragraph spanning pages 5-6 of the Office Action dated July 19, 2007. The applicants note that an absence of exemplified hydrates and solvates does not per se lead to a conclusion that solvates do not exist and can not be made.

Vippagunta et al. states that "approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates" (page 15, left column). Thus, the Office Action's suggestion that solvates and hydrates of the claimed compounds cannot exist is unfounded and unlikely.

The applicants further submit that there is no requirement for the application to describe methods for making solvates and hydrates and no need to show actual examples of the same because what is well known in the art need not be taught in the specification. One of ordinary skill in the art could make and use the claimed solvates and hydrates without such exemplification. Preparation of hydrates and solvates, as discussed at great length above, is well known in the art. The attached Guillory

reference shows the well-known and routine nature of preparing hydrates and solvates. Thus, the present application need not describe any working examples or methods for making solvates and hydrates, since what is well-known need not be taught and one of ordinary skill in the art would know how to make and use the claimed solvates and hydrates.

With respect to the Office Action's contention that the amount of experimentation would be extremely large and therefore undue in view of the millions of compounds encompassed by the claimed genus, Applicant's respectfully note that the courts have repeated held that a large amount of experimentation is not undue if it is merely routine. In re Wands, PPG Indus., Inc. v. Guardian Indus. Corp., 37 USPQ2d 1618, 1623 (Fed. Cir. 1996). As discussed above, making solvates and hydrates is well-known and routine and, thus, preparing hydrates and solvates of the presently claimed compounds would not be undue no matter the quantity.

As the preparation of hydrates and solvates involves the use of well known methods and would not require undue experimentation, and as patents are routinely issued with claims to hydrates and solvates, the applicants respectfully submit that the presently claimed invention to solvates are supported by an enabling disclosure and withdrawal of the Section 112, first paragraph "enablement", rejection of the claims based on the same is requested.

The Section 112, first paragraph "enablement" , rejection of claims 169-173 stated on pages 8-10 of the Office Action dated July 19, 2007 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the teaching of both cell based data and in vivo data on pages 190-193 of the specification, for

example, which demonstrates the making and using of the claimed invention to, for example, inhibit HDAC in a cell, treat a condition mediated by HDAC, treat a proliferative condition, and treat cancer.

Withdrawal of the Section 112, first paragraph "enablement", rejection of claims 169-173 is requested.

The Section 112, second paragraph, rejection of claims 80, 118 and 142, is obviated by the above amendments. Withdrawal of the rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

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